ORIGINAL ARTICLE

Application of the functional Magnetic Resonance Imaging (fMRI) for the Assessment of the Primary Auditory Cortex Function in Partial Deafness Patients – A preliminary study

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Objective: Aim of this study was to evaluate auditory cortex responses to chirp stimulation in patients with partial deafness. Auditory cortex functioning is an important factor of successful rehabilitation after cochlear implantation, particularly in partially deafened patients who have to integrate the natural acoustic hearing with the electric one. This subject has not yet been properly recognized, especially regarding the auditory cortex' tonotopic organization in such patients.

Method: Material included 20 patients referred for the Partial Deafness Treatment – Electric Complement (PDT-EC according to Skarzynski's PDT Classification). fMRI was performed with 3T MAGNETOM TRIO scanner. Subjects were presented with chirps of two bandwidths: 50-950 Hz (middle frequency 500Hz) and 3000-5000Hz (middle frequency 4000 Hz) at 90dB (C) via MRI-compatible earphones. SPARSE paradigm was used.

Results: Bilateral auditory cortex activation was observed in response to 500Hz frequency sounds. No significant activations were found in response to 4000 Hz for p<0.05 with FWE correction; some activations for lower threshold were found.

Conclusions: Paradigm applied in this study gives stable and reproducible auditory cortex responses. fMRI can be considered as method of assessing residual hearing function in auditory cortex of partially deafened patients. Cortical activity in PDT-EC candidates reflects hearing levels determined before study; patients demonstrate residual cortex capacity in response to detected frequency.

Introduction

Hearing disorders are a serious issue in modern society. Hearing deficits affect social behavior, render routine communication difficult, and drastically reduce the quality of life. This is especially important for infants during the critical period of language acquisition [1,2]. The second half of last century saw development of various devices designed to improve or restore hearing [3,4,5,6]. One was the use of electrical stimulation by a cochlear implant (CI) in patients with profound hearing loss. The first CI implantation was performed over 40 years ago [3,4] and many cochlear implant programs have been conducted since [7,8]. Other developments, including soft electrodes to preserve the internal structures of the cochlea, have been introduced into clinical practice [8,9]. However, there is still a large group of patients with significant levels of low

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frequency hearing loss who remain beyond the scope of effective treatment with hearing aids alone.

These patients have significantly impaired hearing: they cannot communicate effectively in everyday situations and have difficulty in understanding speech in noise. This condition has been termed "partial deafness" (PD). Previously, cochlear implantation in PD patients had been contraindicated due to the fear that the procedure may damage remaining cochlear function and cause complete hearing loss. However, the round window approach achieves superior levels of hearing preservation compared to "conventional" cochleostomy [7].

In 2002 the first successful cochlear implantation in a PD patient was performed [10]. Testing showed significant improvement in speech discrimination and communication skills, pointing to the benefits of CI in the PD group [11]. Further research gave rise to a more elaborate concept of Partial Deafness Treatment (PDT) [12], a scheme which aims to distinguish patients differing in their abilities to hear low and high frequencies [7, 8, 9, 11].

One of the group of patients is the PDT-EC group (Fig. 1b) [12,13] which has relatively good hearing at low frequencies (up to 1000–1500 Hz) where no acoustic amplification is required; at the same time, high-frequency regions of

the cochlea still need assistance and can be stimulated electrically with a cochlear implant electrode array, such as the Med-El M, FlexEAS, Standard, and FlexSOFT devices (Med-El, Innsbruck, Austria), which have 20 mm insertion depth, and recently the Cochlear CI422 (formerly SRA) [7,8,9] (Cochlear Ltd., Sydney, Australia), with a 28 mm insertion.

The underlying brain mechanisms of impairment in PDT patients are not yet fully understood. In particular, it is not clear how different types of hearing loss are reflected in the tonotopic organization of the auditory cortex. Furthermore, factors predicting CI outcomes remain to be elucidated. Although CI provides significant benefits to most congenitally deaf children and adults with post-lingual deafness, speech tests after implantation still show large variability [14].

Duration of deafness seems to be a large factor contributing to implantation outcomes but the remaining variability remains unexplained. Recent studies have suggested that the crucial factor for determining CI prognosis may be related to pre-operative measures of metabolic activity in the auditory cortex [15, 16].

Therefore, to allow a wider range of PD patients to benefit from CI, new methods providing a more detailed picture
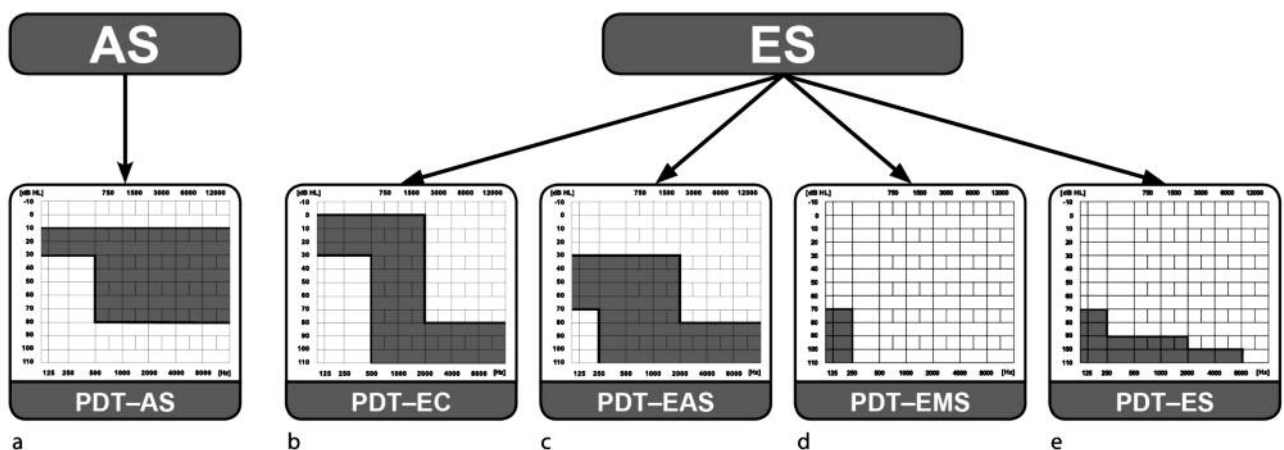
Figure 1. Skarzynski's Partial Deafness Treatment (PDT) classification in which patients are divided into 5 groups based on audiometric criteria. a) PDT-AS (acoustic stimulation) – patients with minimal to severe hearing loss who can be satisfactorily fitted with hearing aids. b) PDT-EC (electrical complement) – patients with normal or slightly elevated thresholds at low frequencies and almost total deafness at higher; non-amplified low-frequency hearing is complemented by electric stimulation at higher frequencies with a cochlear implant. c) PDT-EAS (electric-acoustic stimulation) – patients with mild-to-severe hearing loss at low frequencies and profound hearing loss at high frequencies; low-frequency hearing is amplified and combined with electric stimulation in the same ear. d) PDT-EMS (electric modified stimulation) – used solely in the implanted ear for patients with loss of low-frequency hearing after implantation or with nonfunctional hearing preservation e) PDT-ES (electric stimulation) – patients with non-functional residual hearing; the partial deafness cochlear implantation (PDCI) method is used to preserve cochlear structure.

of auditory cortical processing have much to contribute. In particular, an objective measure of higher auditory cortical processing (including the primary auditory cortex, PAC) would be valuable. Recently, there has been a surge of interest in neuroimaging techniques that could potentially provide an objective test of the integrity of central auditory pathway [17].

Studies using positron emission tomography (PET) have suggested that speech outcome after CI may be predicted on the basis of brain organization examined before surgery [16,18]. It was suggested that hypometabolism of the auditory cortex is associated with better speech perception after implantation. It was also shown that the effectiveness of auditory language learning after CI is associated with the size of the region dedicated to hearing: the larger, the better [16].

Lee et al. [16] used PET to measure, in complete silence, spontaneous brain activity of congenitally deaf children. The study revealed that profoundly deaf subjects who recruit fronto-parietal networks, and in particular the left prefrontal area, during spontaneous brain activity benefit from CI more than subjects engaging posterior-ventral cortices, in particular right-sided temporal regions.

In addition, neuroimaging methods may help to detect whether the superior temporal regions in deaf patients still respond to auditory stimulation, or if, due to cross-modal reorganization, functional take-over by an alternative cognitive process has taken place [22].

Cross-modal reorganization refers, in the auditory domain, to the condition when the auditory cortex is activated in response to stimuli other than acoustic ones, e.g. visual [19,20]. This process can be triggered by auditory deprivation. When functional take-over takes place, the auditory association areas in superior temporal regions are no longer dedicated to auditory stimulation, even though the PAC can still respond to electrical stimulation of the auditory nerve [21].

Although PET studies may provide new insights into our understanding of the therapeutic success of CI, the technique has a number of inherent limitations, among which radiation exposure appears to be the most serious. However, this limitation does not apply to the functional magnetic resonance imaging method (fMRI), which uses the paramagnetic properties of deoxyhemoglobin and the diamagnetic properties and oxyhemoglobin to detect focal brain activity at high spatial resolution. In auditory studies, fMRI has been used to measure changes in the blood oxygenation level dependent signal (BOLD) elicited by acoustic stimulation. This objective and noninvasive tool may complement diagnostic instrumentation used to evaluate various aspects of peripheral hearing acuity and sensory functions [23]. Although there are many fMRI studies examining the auditory cortex's response to speech, words, pure tones, and music in healthy people, only a few research groups have conducted fMRI studies to investigate PAC functions in deaf patients [23,24]. Patel et al. [23] and Neumann et al. [25] suggested that, in hearing-impaired infants and children, the amount of auditory cortex activity as shown by fMRI is related to improvements in post-operation hearing abilities measured after CI. Lazard et al. [24] used the fMRI technique to complement available behavioral data and tried to predict the outcomes of cochlear implantation in patients with post-lingual deafness. The study suggested that patients whose implants worked effectively recruited different brain networks while processing speech compared to patients who failed to benefit from the surgery.

Existing studies suggest that fMRI may help predict whether substantial communication benefits from CI may occur in hearing-impaired patients. The use of fMRI is three-fold:

1) it may help assess the neural strategies involved in processing sound which underlie brain plasticity, strategies connected with radiological and electrophysiological assessment after cochlear implantation (a stage at which fMRI is not possible) [24];

2) it may provide additional information about the integrity of auditory pathways [8];

3) it may serve as a method of assessing residual function in the PAC due to possible change in its tonotopy during long-term partial deafness [23,25].

Nevertheless, little is known about auditory cortex responses in patients with residual hearing. It remains an open question whether activity in the auditory cortex depends on the extent of hearing loss [26].

The current study aims to explore this lacuna. According to our knowledge, it is the first study which uses the fMRI technique to study brain activity in response to chirps in patients classed as PDT-EC [11].

Materials and Methods

All participants of this study provided informed consent in compliance with the Code of Ethics of the World Medical Association (Helsinki Declaration) and methods approved by the local Bioethics Committee were followed (application no IFPS/KB/08/2010).

Subjects

Exactly 20 patients with partial deafness, aged from 12 to 75 years (M=42.7 years; SD=17.5), participated in this study. Prior to the fMRI experiments, the patients underwent audiological testing including pure tone audiometry with standard frequencies of 125, 250, 500, 1000, 2000, 4000, and 8000 Hz. On the basis of their audiograms the patients were classified as fitting the partially deaf electrical complement category, EC. All 20 patients had similar audiometric profiles in both ears, and the mean audiogram for both ears is presented in Figure 2.

Study Design

Subjects were presented with two sets of chirps that had center frequencies important from the point of view of cochlear implant candidates: 500 Hz (bandwidth 50–950 Hz) and 4000 Hz (bandwidth 3000–5000 Hz). Stimuli were presented at 90 dB(C) via MRI-compatible earphones. The study used a Sparse paradigm, which is made clear by inspection of Figure 3. There was a basic 15 second repetitive time frame, during which whole brain images were acquired for 3 seconds. During acquisition, the MRI scanner generated a noise of 99 dB SPL (attenuated to ca. 80 dB SPL by the headphones). During each 5-second period before acquisition, three

repetitions of a 1-second chirp were presented. Because there is a delay in the hemodynamic response (it reaches a maximum value ca. 5–6 seconds after a stimulus), the maximum response to a given stimulus is expected at the moment of image acquisition. The following 5-second period, during which image acquisition is not preceded by a chirp, serves as a reference to the stimulus acquisition period. The stimuli were synchronized with image acquisition to 1 ms accuracy.

The study was performed in a 3T Magnetom Trio scanner (Siemens AG, Erlangen, Germany). T1-weighted structural images were acquired with isotropic voxel size of 0.9×0.9×0.9 mm. Two functional 'runs' were acquired with TR=18,000 ms and TE=30 ms. A single volume was acquired as fast as possible during each TR period (about 3000 ms for 48 slices from the beginning of a TR period), so until the end of the TR period there was no acoustic noise generated by gradients. Functional data was obtained with a gradient-echo EPI sequence. Each functional series contained 50 volumes (each volume consisted of 48 slices, and the signal was acquired with a physical matrix of 64×64). Voxel size for functional images was 3×3×3 mm. Morphological images of the whole brain were also obtained using standard T2-weighted sequences to exclude neurological pathology. In two cases examinations had to be repeated due to patient activity during examination. Normally, the patient was placed in the MRI device in a way that made movement impossible. Due to the paradigm used, there was no need for other restrictions like closing of eyes, etc.
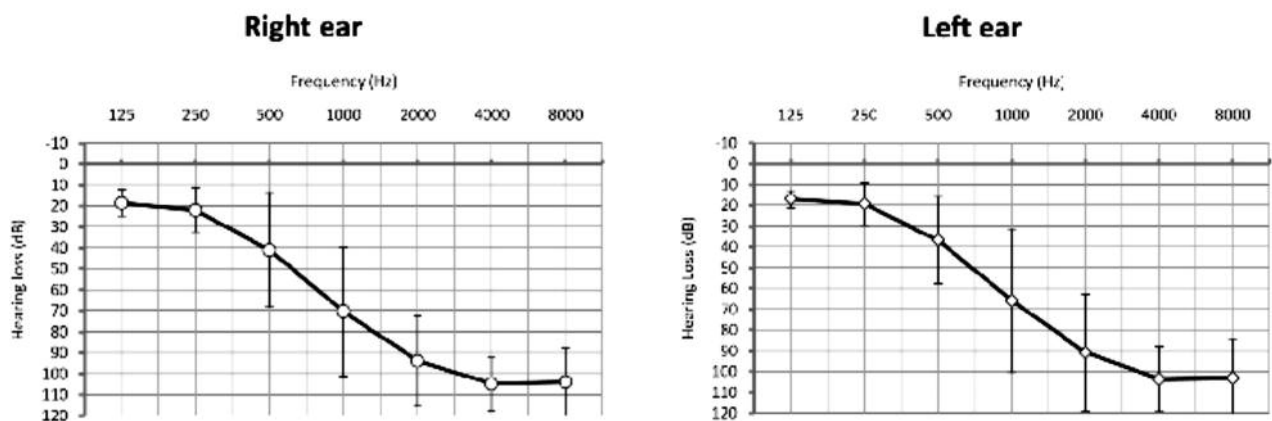
Figure 2. Mean audiograms (right and left ears) of 20 patients classified as having partial deafness (electrical complement). Bars show standard deviations.
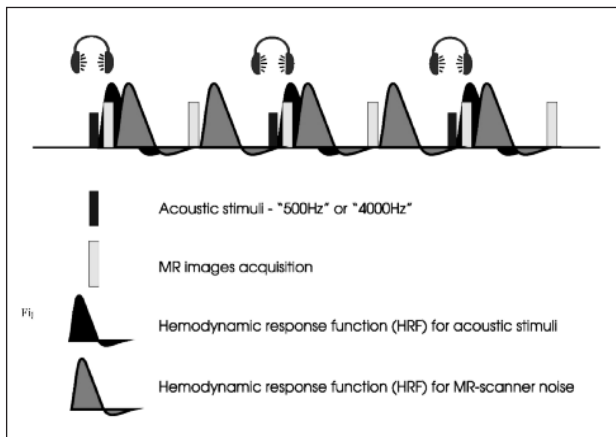
Figure 3. The Sparse study paradigm.

Data Analysis

The fMRI data was analyzed using the SPM8 package (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/) and Brain Voyager QX. Data preprocessing comprised the following three steps: 1) motion correction to eliminate motion artifacts and correction of geometric distortion of the EPI images caused by the inhomogeneity of the head; 2) normalization of the brain images to enable comparisons between patients group; and 3) smoothing filters were applied to decrease the morphological differences between subjects. Two stages of analysis were performed: first, a single subject analysis (SSA) and secondly a multi subject analysis (MSA). Data was then prepared for Pearson correlation analysis: on the basis of average normalized results from all patients a mean activation was obtained and used to determine a mask for the primary and secondary auditory cortex areas.

Then for each patient the voxels for which the significance level was less than 0.001 (uncorrected *p* value) were extracted. For each voxel the course of the BOLD signal was determined. The BOLD signal in particular voxels in the area of the previously established mask was averaged separately for the left and right auditory cortex. Calculation of *t*-statistics and percentage signal change was then done. The percent of BOLD signal change is proportional to the amount of neural activation (25). For each patient four values of the BOLD percent signal change were determined separately for left and right hemispheres and for low (500 Hz) and high (4000 Hz) frequencies.

The second level analysis (one sample *t*-test) was conducted separately for low and high frequencies. In addition, Pearson correlations between the percentage of BOLD signal change in the region of interest (i.e. the left and right auditory cortex) and the audiograms in the contralateral ear were calculated separately for low and high frequencies. More specifically, the pure tone average for low frequencies (PTA_{low}) (125, 250, 500, and 1000 Hz) was obtained for each patient separately for left and right ears. These results were then correlated with the percent of BOLD signal change evoked by a 500 Hz chirp in the contralateral auditory cortex. For high frequencies, a weighted mean of 4000 Hz and 2000 Hz (with a higher contribution from the former) was obtained in each patient separately for left and right ears to give PTA_{high}. Then the correlations between these values and the percentage BOLD signal change in response to a 4000 Hz chirp in the contralateral auditory cortex were calculated.

Results

As expected, bilateral activation in the auditory cortex was observed in response to stimulation with 500 Hz chirps. For 4000 Hz chirps, there was a small group effect ($p<0.05$, Family Wise Error corrected), and there were some significant activations for lower thresholds ($p<0.001$, uncorrected). An example of the results of tests for low and high frequencies in one of the subjects are presented in Figure 4. Higher *t*-values (yellow) mean that there is a high probability that this region was activated by the stimuli. Together, the collected data indicate that the paradigm developed for this study gives stable and reproducible responses of the auditory cortex.

As described above, Pearson correlations between the percentage of BOLD signal change in the regions of interest (i.e. left and right auditory cortex) and the PTA_{low} and PTA_{high} values from the ipsi- and contralateral ears were calculated (Figure 5). In the EC group significant negative correlations were found only for low frequency stimulation. More specifically, hearing loss in the left ear correlated ($r = -0.58$, $p < 0.05$) with the percent of BOLD signal change in the contralateral auditory cortex. In the right ear, hearing loss was significantly associated with both contra- and ipsilateral auditory cortex activations ($r = -0.61$, $p < 0.05$ and $r = -0.54$, $p < 0.05$, respectively).
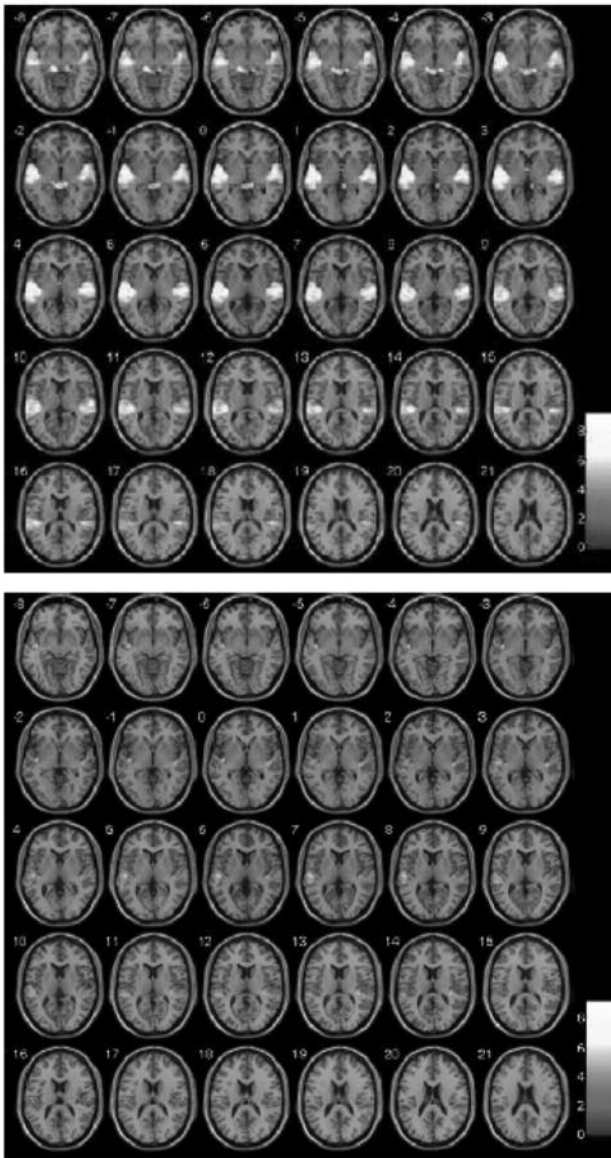
Figure 4. Brain activation in response to low frequency (upper) and high frequency (bottom) chirps for one subject in the EC partial deafness treatment group (p<0.001, uncorrected).

Discussion

This study is the first to apply fMRI to investigate BOLD signal changes in the auditory cortex induced by chirp stimulation in patients with partial deafness (PDT-EC candidates). The data agree with the existing, but scarce, neuroimaging literature which shows that fMRI can be used to detect central auditory activation in patients with differing levels of hearing loss [23, 27, 28].

Our results show that fMRI is not an ideal way to study all aspects of auditory cortex functioning in candidates for partial deafness treatment. However, it is a useful beginning, and other studies are in train to evaluate the effectiveness of other techniques such as auditory evoked magnetic fields.

In this study, patients selected for PDT-EC intervention showed BOLD responses within the bilateral superior temporal gyri (STG) in response to 500 Hz, but not to 4000 Hz (when corrections were made for multiple comparisons using few, which provides very strict criteria). At the same time, when a less strict threshold is used, it indicates that there are significant voxels which respond to 4000 Hz [29, 30, 31, 32]. Further analysis showed that, for low frequency sound stimulation, the percent signal change of the BOLD response in the auditory cortex was significantly correlated with PTA_{low} and PTA_{high}.

In summary, the cortical activity of PDT-EC candidates correlated with their hearing level, indicating that patients have a residual cortex capacity to respond to the stimulus frequencies.

Some studies have shown correlations between auditory activation, demonstrated by fMRI before CI, and an improvement in the audiological assessment after CI [23]. These results suggest that the capacity of the auditory cortex may be a key prognostic factor in the prediction of CI outcomes. In the same way, our study shows that PDT-EC candidates generate cortical activity in response to auditory stimulation.

Our study involved PDT-EC candidates only, but further on-going research will assess central auditory processing in the remaining PD candidacy groups. We have applied the same protocol to study PDT-ES and PDT-EAS candidates, and some preliminary results have been presented for a small group of patients [32,33]. The PDT classification is a relatively new concept and larger cohorts of patients will be recruited in the near future using this scheme. Another aim will be to investigate whether age and the duration of deafness might significantly affect activity of the auditory cortex.

These results are promising and deserve further attention. They have encouraged the authors to undertake further studies of CI-candidates in which behavioural auditory measurements are being correlated with central auditory activity evaluated with fMRI. The next step of the analysis will involve correlating post-implantation outcomes in language tests with pre-implantation BOLD responses.
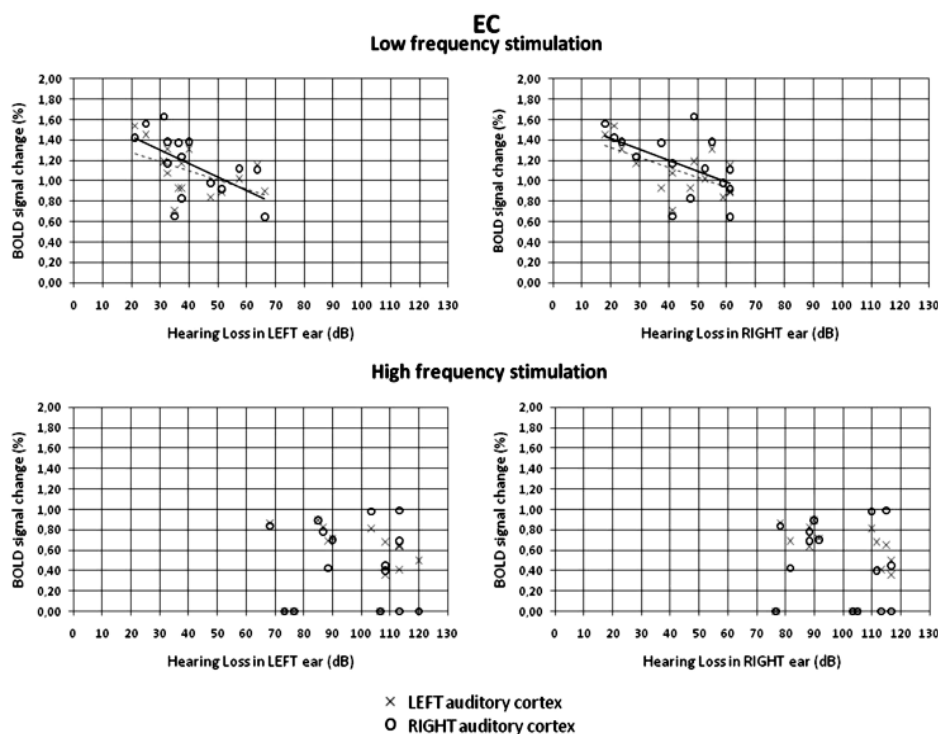
Figure 5. Scatterplots showing correlations between hearing loss and BOLD signal change in the auditory cortex for the EC partial deafness treatment group (p < 0.05; FWE corrected, k ≥10 voxels). The results are limited to the 15 of 20 patients who agreed to share their audiograms.

This will provide detailed characteristics of cortical activity within PD patients in the context of providing a prognosis for CI outcomes.

In conclusion, our preliminary results show that fMRI can be successfully applied to examine BOLD signal changes in the auditory cortex induced by chirp stimulation in patients with partial deafness. Importantly, fMRI can be considered as an objective method of assessing residual function of auditory cortex in PD patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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